GABA Modulating Agents: A Brief Review

A.P.G. Nikalje, M. Ghodke and A. Girbane
Department of Pharmaceutical Chemistry, Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rauza Bagh, P.B. No. 33 Aurangabad (M.S.) 431001, India

Corresponding Author: Anna Pratima G. Nikalje, Department of Pharmaceutical Chemistry, Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rauza Bagh, P.B. No. 33 Aurangabad (M.S.) 431001, India
Tel: +91 9823619992 Fax: +91 240 2381129

ABSTRACT
The search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of intensive investigation in medicinal chemistry. Moreover, many serious side effects are reported in many patients treated with presently available antiepileptic drugs (AEDs). In India, studies have reported the prevalence rate of epilepsy varying from 1710 to 9780 cases per million populations. Despite the optimal use of available antiepileptic drugs (AEDs), many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects. The limitations with the conventional AEDs highlighted the need for developing newer agents for epilepsies and the AED search has come a long way, particularly over the last two decades. This review describes new antiepileptic agents representing various structures for which the precise mechanism of action is still not known. New antiepileptic drugs increase the spectrum of treatment and represent further steps with regard to the optimization of an individual therapy of the epilepsies. Here we are providing the review of novel GABA modulating agents, which seem to be effective when evaluated for their antiepileptic activity.

Key words: Anticonvulsant agent synthesis, GABA nergics, epilepsy, seizures

INTRODUCTION
Epilepsy is not a disease, but a syndrome of different cerebral disorders of the Central Nervous System (CNS), which is characterized by paroxysmal, excessive and hypersynchronous discharges of large numbers of neurons. Epilepsy is one of the most common serious neurological disorders characterized by recurrent seizures. It results from a temporary electrical disturbance of the brain due to an imbalance between excitatory and inhibitory neurotransmitters. However, 30% of epileptic patients continue to have seizures despite optimized treatment with classical antiepileptic drugs (AEDs).

Epilepsy is a chronic neurological disorder characterized by the periodic and unpredictable occurrence of seizures that affects the people of all ages. Being one of the world’s oldest recognized disorders, it is surrounded by fear, discrimination, social and frightening manifestation. There are five broad categories of epileptic seizures, the subtypes and their characteristics are summarized in Table 1. A global campaign against epilepsy conducted by World Health Organization (WHO) in partnership with International Bureau for Epilepsy (IBE) and International League against Epilepsy (ILAE) suggests that around 1% of world population at any time (about 50 million people worldwide) is afflicted with this neurological disorder. Every year about 2.4 million new cases are
Table 1: Types of epileptic seizures (Katzung, 2006; Allen et al., 2006; Tripathi, 2004)

<table>
<thead>
<tr>
<th>Seizure types</th>
<th>Seizure characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized</strong></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic</td>
<td>Tonic rigidity of extremities, massive clonic jerking, urinary incontinence, onset at any age</td>
</tr>
<tr>
<td>Simple absence</td>
<td>Sudden loss of consciousness up to 30 sec, clonic jerking of eyelids, onset between 3-10 years</td>
</tr>
<tr>
<td>Myoclonic kreeting</td>
<td>Sudden violent contraction of extremities, with or without loss of consciousness, onset between 5-20 years</td>
</tr>
<tr>
<td>Atomics/ akinetic</td>
<td>Sudden loss of muscle tone lasting 10-60 sec, onset between 1-5 year</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td></td>
</tr>
<tr>
<td>Simple seizure</td>
<td>Convulsant confined to single limb or muscle, no impairment of consciousness, onset at any age</td>
</tr>
<tr>
<td>Complex seizure</td>
<td>Confused behavior, loss of consciousness, last for several minutes, onset at any age.</td>
</tr>
<tr>
<td>Unilateral seizure</td>
<td>In this class only one entire side of the body is affected</td>
</tr>
<tr>
<td>Erratic seizure</td>
<td>This class of seizure observed in newborn</td>
</tr>
<tr>
<td>Unclassified seizure</td>
<td>This class of seizure is due to any unidentified origin different from listed I to IV</td>
</tr>
</tbody>
</table>

Table 2: Classification of anticonvulsant agents (Katzung, 2006; Allen et al., 2006; Tripathi, 2004)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbbiturates</td>
<td>Phenobarbital,</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>Facilitation of GABA mediated Cl⁻ channel opening.</td>
<td></td>
</tr>
<tr>
<td>Hydantoin</td>
<td>Phenytoin.</td>
<td></td>
</tr>
<tr>
<td>Mephenytoin</td>
<td>Prolongation of Na⁺ channel inactivation.</td>
<td></td>
</tr>
<tr>
<td>Oxazolidenediones</td>
<td>Phenytoin, phenobarbital,</td>
<td>inhibition of T type Ca⁺ current</td>
</tr>
<tr>
<td>Succinimides</td>
<td>Ethosuximide.</td>
<td></td>
</tr>
<tr>
<td>Phensuximide</td>
<td>Inhibition of T type Ca⁺ current.</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam,</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Facilitation of GABA mediated Cl⁻ channel opening.</td>
<td></td>
</tr>
<tr>
<td>Dibiprop carboxylic acids</td>
<td>Sodium valproate</td>
<td>All the three mechanisms</td>
</tr>
<tr>
<td>Iminosibilebenes</td>
<td>Carbamazepine, oxcarbazepine</td>
<td>Prolongation of Na⁺ channel inactivation</td>
</tr>
<tr>
<td>Cyclic GABA analogues</td>
<td>Gabapentin.</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Facilitation of GABA mediated Cl⁻ channel opening.</td>
<td></td>
</tr>
<tr>
<td>Acetazolamides</td>
<td>Sultiane,</td>
<td>Carbonic anhydrase inhibitor</td>
</tr>
<tr>
<td>Newer drugs</td>
<td>Vigabatrin</td>
<td>Facilitation of GABA mediated Cl⁻ channel opening</td>
</tr>
<tr>
<td></td>
<td>Topiramide, Lamotrigine</td>
<td>Prolongation of Na⁺ channel inactivation</td>
</tr>
</tbody>
</table>

added to these data. The classification of antiepileptic agents along with the examples and their mechanism of action are presented in Table 2. Currently available antiepileptic drugs (AEDs) provide adequate seizure control in many patients; still about 28-30% of patients are estimated to be poorly treated. Much efforts devoted in the recent years for the development of novel therapeutics resulted in the availability of several newer drugs (such as pregabalin, stiripentol, zonisamide, tiagabine, lamotrigine, levetiracetam, topiramate) as promising anticonvulsants. These drugs have proven to be effective in reducing seizure, whilst their therapeutic efficacy is overcome by some undesirable side effects such as headache, nausea, hepatotoxicity, anorexia, ataxia, drowsiness, gastrointestinal disturbances and hirsutism. These observations affirm the further scope and need for the development of newer agents (Ammerkar and Bhusari, 2010).

γ-Amino Butyric Acid (GABA) has been known to be present in plants and bacteria for almost a hundred years and the decarboxylase catalyzing its formation from glutamate was described in bacteria early on Steward et al. (1949). Its presence in brain tissue together with its biosynthetic enzyme glutamate decarboxylase (GAD) was described simultaneously in three independent publications in 1950 (Awapara et al., 1950). One of the first indications that GABA could play an
Fig. 1: Mechanism of action of anticonvulsant agents

An important role in brain function came from studies with the convulsant hydrazides which inhibit its synthesis (Killam, 1957) and the demonstration by Bazemore et al. (1957) that a factor in brain extracts that caused an inhibitory action at the crayfish stretch receptor was actually GABA. Further elegant electrophysiological studies soon confirmed that GABA was indeed an important inhibitory neurotransmitter (Curtis et al., 1959). The peripheral administration of GABA can not be usefully performed since this neurotransmitter is able to cross the Blood Brain Barrier (BBB) only when extremely high doses are applied, which produce severe adverse side effects (Toth et al., 1983). Hence, over the past few decades, research aimed at achieving successful delivery of GABA into the CNS has resulted in the discovery of various GABA analogs with improved pharmacological activities (Yogeewari et al., 2006).

**Mechanism of action**: Barar (2003), Wilson et al. (2004), Kadam et al. (2003) and Stefan and Feuerstein (2007). Mechanism of action of anticonvulsant agents can be divided in three main categories as shown in Fig. 1 and is described as follows:

**Prolongation of sodium channel inactivation**: Many drugs preferentially block the N channels that remain open due to repetitive neuronal firing, i.e., they block the use-dependent or voltage-dependent Na channels. The higher the frequency of the firing the greater is the block. When as neuron fires, the Na channel passes through its active-inactive and resting phases. These antiepileptic drugs the duration of inactivated phase and delay its reversion to the resting phase. This reduces their chances of becoming available for activation again. Examples of drugs are Phenytoin, Carbamazepine, Lamotrigine, Lidocaine etc.

**Facilitation of GABA mediated Cl⁻ action**: GABA, γ-aminobutyric acid is the principal inhibitory neurotransmitter in the mammalian brain. It has been estimated that approximately 40% of synapses in the CNS are GABAergic. It is well documented that attenuation of GABAergic neurotransmission is involved in pathophysiology of several CNS disorders in humans namely anxiety, pain, epilepsy, depression and mania (Bell and Sander, 2002).

GABA is synthesized by the enzyme glutamic acid decarboxylase (GAD, pyridoxal phosphate-(PLP)-dependent) which acts on glutamate and removes the gamma-carboxyl group as CO to produce GABA (Sherif et al., 1997).

Examples of drugs are Benzodiazepines, Barbiturates, Tigabine, valproate, Zonisamide etc.
Inhibition of T-type calcium current: Ethosuximide is a major drug used for the treatment of absence seizures. It inhibits the low threshold Ca\(^{2+}\) currents carried by T-type Ca\(^{2+}\) channels. T-type Ca\(^{2+}\) currents are responsible for generation of the thalamic cortical in petit mal attack. Inhibition or reduction of the low threshold T-type Ca\(^{2+}\) channels therefore, could account for the seizure specific therapeutic action of ethosuximide. Examples of other drugs are Valproate, Zonisamide etc.

LITERATURE SURVEY

Serfass and Casara (1998) has performed the stereospecific synthesis of cis and trans 3-substituted vinyl-\(\gamma\)-aminobutyric acid analogs were obtained by either a Claisen rearrangement or a Wittig reaction from common diene precursors and found the very potent anticonvulsant activity.*

![Cis and trans 3-substituted vinyl-\(\gamma\)-aminobutyric acid analogs](image)

Trapani et al. (2003) has synthesized the alpidem analogues containing a GABA (1-3) or glycine (4-6) moiety and evaluated their interaction with the GABA/benzodiazepine receptor complex at central (CBR) and peripheral (PBR) level. In particular, their ability to modulate the specific binding of [H]-GABA to washed membrane preparations from the rat cerebral cortex, as well as their effects on human recombinant GABA receptors in Xenopus laevis oocytes, were assessed.

Bolvig et al. (1999) has investigated the inhibitory action of bicyclic isoxazole-\(\gamma\)-aminobutyric acid (GABA) analogues and their 4,4-diphenyl-3-buteryl (DPB) substituted derivatives in cortical neurones and astrocytes as well as in human embryonic kidney (HEK 293) cells transiently expressing either mouse GABA transporter-1 (GAT-1), GAT-2, -3 or -4. It was found that 4,5,6,7-tetrahydroisoxazolo[4,5-c] pyridin-3-ol (THPO) and 5,6,7,8-tetrahydro-4H-isoxazolo [4,5-c] azepin-3-ol (THAO) displayed some inhibitory activity on GAT-1 and GAT-2, where the compounds exhibited a slightly lower potency on GAT-2 compared to GAT-1.

![5,6,7,8-Tetrahydro-4H-isoxazolo [4,5-c] azepin-3-ol derivatives](image)

Rasmus et al. (2005) synthesized a series of lipophilic diaromatic derivatives of the glia-selective GABA uptake inhibitor (R)-4-amino-4,5,6,7-tetrahydrobenzo[d]isoxazol-3-ol (R)-exo-THPO. The effects of the target compounds on GABA uptake mechanisms in vitro were measured using a rat
brain synaptosomal preparation or primary cultures of mouse cortical neurons and glia cells (astrocytes), as well as HEK cells transfected with cloned mouse GABA transporter subtypes (GAT1-4).

Ana et al. (2008) has described the synthesis of sugar-fused b-disubstituted c-butyrolactones, c-butyrolactams and a lipophilic b-disubstituted GABA analogue as potential GABA receptor ligands, where the pharmacophore is engineered into the carbohydrate scaffold in the form of a C-fructoside. The products were characterized for receptor binding studies of GABA-A receptors.

Jegadeesan et al. (2007) designed and synthesized two series of pharmacophoric hybrids of phthalimide GABAanilides/hyrazones and evaluated for their anticonvulsant and neurotoxic properties. All of the compounds were ineffective in the MES test. Most of the compounds were found to be effective in the scSTY and ipPIC models and very few compounds showed protection in the scPTZ model.

Natalie et al. (2002) carried out the condensation of cyclic 1,3-diketo esters with 3- and 5-aminoisoaxazole derivatives which led to a series of potent anti-maximal electroshock (MES) analogues, three of which occurred in the 3-amino series: ethyl ester (10), orally (po) active in rats [ED50 68.9 mg kg\(^{-1}\), TD50>500 mg kg\(^{-1}\), protective index (PI=TD50/ED50) >49.6]; methyl ester (9), ED50 68.9 mg kg\(^{-1}\) intraperitoneally (ip) in mice, TD50>500 mg kg\(^{-1}\), PI>7.3 and tert-butyl ester (8), ED50 28.1 mg kg\(^{-1}\) po in rats, TD50>500 mg kg\(^{-1}\), PI>17.8.

Arne et al. (2004) has studied the identification and subsequent development of the GABA transport inhibitor tiagabine which has confirmed the important role that GABA transporters play in the control of CNS excitability. Tiagabine was later demonstrated to be a selective inhibitor of the GABA transporter GAT1.
Long et al. (2004) has performed the development of new anticonvulsive agents, analogs of γ-vinyl GABA (vigabatrin) containing GABA, -vinyl GABA, valproic acid, nipecotic acid or isonipecotic acid moieties were prepared and evaluated for their anticonvulsive activities. Most of the prepared compounds showed moderate anticonvulsive activities. Among them compounds 10 and 16 displayed the most potent anticonvulsive activity and a broader spectrum compared to vigabatrin.

Jan et al. (1999) have synthesized piperidinyl-3-phosphinic acid, piperidinyl-3-methylphosphinic acid and N-(4, 4-diphenyl-3-butenyl)-piperidinyl-3-phosphinic acid as bioisosteres of the corresponding amino carboxylic acids, which are potent and specific GABA-uptake inhibitors. The novel amino phosphinic acids were tested for their GABA uptake inhibitory activity.

![N-(4,4-Diphenyl-3-butenyl)-piperidinyl-3-phosphinic acid](image)

Jegadeesan et al. (2008) has reported design and synthesis of newer γ-aminobutyric acid (GABA) derivatives with the combination of thiosemicarbazone and GABA pharmacophores in order to develop newer anticonvulsants.

![Thiosemicarbazone derivatives of GABA](image)

Cunde et al. (2007) studied many different 3α-hydroxysteroids in the androstane and pregnane steroid series enhance the actions of γ-aminobutyric acid (GABA) at GABA type-A (GABA-A) receptors in the mammalian central nervous system.

Gabriella et al. (2008) reported the synthesis and binding studies of a series of 3-acylpyrazolo [5,1-c][1,2,4]benzotriazine 5-oxides. High-affinity ligands at benzodiazepine site on GABAA receptor complex (GABAA/ß3R complex) were obtained when the 3-acyl substituent is represented by a five-member heteroaroyl ring (furoyl*, thenoyl* and pyrroyl*).

![3-Acylpyrazolo[5,1-c][1,2,4]benzotriazine 5-oxides](image)

Rujee et al. (2004) has synthesised E-4-Amino-2-methylbut-2-enoic acid, (±)-4-amino-2-methylbutanoic acid, (+)-(S)- and (-)-(R)-4-amino-2-methylbutanoic acid, which are analogues of the inhibitory neurotransmitter GABA from ethyl 2-methyl-4-phthalimidobut-2-enoate,
ethyl 2-methyl-4-phthalimidobutanoate, (±)-(2R-(3,3-dimethylbutylo-1,4-lactonyl))-methyl-4-phthalimidobutanoate and (±)-(2R-(3,3-dimethylbutylo-1,4-lactonyl))-methyl-4-phthalimidobutanoate, respectively.

R and S form of 3,3-Dimethylbutylo-1,4-lactonyl)-methyl-4-phthalimidobutanoate.

Stephen et al. (1997) has synthesized the stereocontrolled conjugate addition of anions derived from chiral α-chlorophosphonamides to α,β-unsaturated esters leads to the corresponding 3-chloroester adducts which undergo intramolecular expulsion of the chlorine atom to give the corresponding cyclopropanes.

Tae et al. (2008) generated pyridoxyl-γ-aminobutyrate (PL-GABA), a novel GABA analogue composed of pyridoxyl and GABA and have also characterized its anticonvulsant and pharmacological functions in vitro. The results of biodistribution studies revealed that PL-GABA is capable of crossing the blood brain barrier. PL-GABA evidenced anticonvulsant activity in a wide range of epilepsy models.

Bailleux et al. (1995) has synthesized a short series of 4-nitro-N-phenylbenzamide and evaluated for anticonvulsant properties and neurotoxicity. In mice dosed intraperitoneally, three of the four 4-nitro-N-phenylbenzamides were efficient in the MES test, especially N-(2,6-dimethylphenyl)-4-nitrobenzamide and N-(2-chloro-6-methylphenyl)-4-nitrobenzamide.

Hans et al. (2007) has prepared and tested a series of 3- and 5-aryl-1,2,4-oxadiazole derivatives for anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles exhibit considerable activity in both pentylenetetrazole (PTZ) and Maximal Electroshock Seizure (MES) models.
Shalini et al. (2009) synthesized a new series of 4,5-diphenyl-2H-1,2,4-triazol-3(4H)-one to study the effect of cyclization of the semicarbazone moiety of aryl semicarbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant.

Gita et al. (2008) have synthesized a series of 6-amino-1,4-oxazepane-3,5-dione derivatives, based on the structural estimations of the typical anticonvulsant drugs, novel structures of 7-membered heterocyclic imides, which were hybridized with pharmacophores such as cyclic imide and N-CO-C-N group in their molecule were designed.

Zhong et al. (2008) has performed the synthesis of a series of 7-benzylamino-2H-1,4-benzoaxazin-3(4H)-ones. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES test). The MES test showed that 7-(4-flurobenzylamino)-2H-1,4-benzoaxazin-3(4H)-one 4b was the most potent with ED50 value of 31.7 mg kg⁻¹ and protective index (PI ¼ TD50/ED50) value of 7.2.

Hilary et al. (2004) has studied Themisone, which is also known as Atrolactamide, was found, in the 1950s, to be a very potent anticonvulsant. It was hypothesized that the -CF3
substitution would maintain the anticonvulsant activity. Therefore, a diverse range of analogues were synthesized utilizing multiple synthetic pathways to explore the structure-activity relationship.

Shindikar et al. (2006) have synthesized a set of seven novel N-substituted 2-anilinophenylacetamides and designed by pharmacophore generation using flexible alignment module of MOE software.

Faizul et al. (2009) designed and synthesized a series of N²-(naphtha[1,2-d]thiazol-2-yl) semicarbazides. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and scPTZ-induced seizure tests and minimal motor impairment was determined by rotorod test.

Nadeem et al. (2007) prepared a series of 1,3-benzothiazol-2-yl semicarbazones (1-15) in satisfactory yield and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screen. Selected compounds were checked for their lipophilic character.

Bajaj et al. (2004) have synthesized a series of 2-substitutedphenyl-3-(substituted phenyl amino) methyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (4a-4p) and 2-substituted phenyl-3-substitutedphenylazo-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (5a-5p) from 2-substitutedphenyl-2,3-dihydro-4-diphenylamino-1,5-benzoxazepines (3a-3d) by the Mannich reaction and diazotation reaction, respectively.
De Sarro et al. (1995) has studied the behavioural and anticonvulsant effects of several 1-aryl-3,5-dihydro-4H-2,3-benzodiazepin-4-ones (2,3-BZs) and of 1-lb-aryl-7,11-dihydro-3-phenyl[1,2,4]oxadiazolo[5,4-a][2,3]benzodiazepin-6-ones (2,3-OBZs) after intraperitoneal (i.p.) administration in DBA/2 mice, a strain genetically susceptible to sound-induced seizures.

Alba et al. (2001) prepared a number of novel 1H-pyrrolo [1,2-a]benzimidazol-1-one derivatives and evaluated their anticonvulsant properties.

Silvana et al. (2004) synthesized a series of new 3-alkylcarbamoyl-1-aryl-3,5-dihydro-7,8-dimethoxy-4H-2,3-benzodiazepin-4-ones starting from the corresponding 3-N-unsubstituted derivatives, previously described as noncompetitive AMPA-type glutamate receptor antagonists.

Kamelia et al. (2008) performed the synthesis of some new substituted coumarinylthiazolines, coumarinylthiazolin-4-ones and substituted chromenethiazoles and evaluated for anticonvulsant activity.

Joshi et al. (2003) synthesized the imidazolinone derivatives obtained by the condensation of some known sulpha drugs with 5-oxazolone derivatives. The products have been screened for their (a) in vitro growth inhibitory activity against several microorganisms and (b) in vivo anticonvulsant activity.
Nicola et al. (2005) synthesized and tested a series of 2-semicarbazonomethyl-4,5-methylenedioxyphenylacetic acids as anticonvulsant agents in DBA/2 mice against sound-induced seizures and the results compared to those previously reported for the corresponding methyl esters.

Yogeeswari et al. (2005) found out the synthetic route for a series of 4-ethoxyphenyl semicarbazones. The anticonvulsant activity of all the synthesized compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice.

Rosaria et al. (2004) synthesized a novel series of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as potential non-competitive AMPA receptor antagonists. When tested for their ability to prevent sound-induced seizures in DBA/2 mice, some of these novel compounds showed high anticonvulsant potency.

Ali et al. (2004) has synthesized and screened a series of new 2-substituted-5-[2-(2-fluorophenoxo) phenyl]-1,3,4-oxadiazoles for their anticonvulsant activities.
Rostock et al. (1996) was evaluated the anticonvulsant activity of the novel drug D-23129 N-(2-amino-4-(4-fluorobenzylamino)phenyl)carbamic acid ethyl ester in animal models of epileptic seizures.

Bonina et al. (2000) found out 7-Chlorokynurenic acid which is a potent glycine-N-methyl-D-aspartate (NMDA) receptor antagonist, but it shows weak activity after systemic administration. In order to overcome the Blood-Brain Barrier (BBB), they synthesized three new esters obtained by chemical conjugation with essential nutrients such as glucose and galactose, that are actively transported across the BBB.

Ghidini et al. (2006) demonstrated that Several studies of N-substituted amino acid derivatives exhibit weak anticonvulsant activities in vivo. In the present study, a series of amides of aminoacids structurally related to aminoacetamide have been synthesised and investigated for anticonvulsant activity.

Obniska et al. (2006b) described the synthesis, physicochemical and pharmacological properties of new N-[(4-arylpiperazin-1-yl)-alkyl]-2-azaspiro[4.4]nonane- and [4.5]decane-1,3-dione derivatives.

Thiry et al. (2008) screened a small library of indanesulfonamides for the inhibition of the human carbonic anhydrase (CA, EC 4.2.1.1) isoforms involved in neuronal excitation. These CA isoforms are becoming interesting target for the design of agents useful for the treatment of epilepsy.

Thirumurugan et al. (2006) synthesized Various 2,4-dimethoxyphenylsemicarbazones starting from 2,4-dimethoxyaniline via a phenylcarbamate intermediate and screened for anticonvulsant activity.
Guo et al. (2009) has synthesized a series of 5-alkoxy-[1, 2, 4]triazolo[4,3-a]quinoline derivatives using 4-hydroxyquinolin-2(1H)-one as the starting material. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES) and their neurotoxicities were measured by the rotarod test.

Sun et al. (2009) synthesized a new series of 8-alkoxy-5, 6-dihydro-[1,2,4] triazino [4,3-a]quinolin-1-one derivatives. Their anticonvulsant activities were evaluated by the maximal electroshock (MES) test and their neurotoxicities were evaluated by the rotarod neurotoxicity test.

Kulandasamy et al. (2009) synthesized thirty nine new 3,4-di(substituted)oxy-N,N-bis (substituted)thiophene-2,5-dicarboxhydrazides starting from ethyl thiodiglycolate through multi-step reactions and screened for the anticonvulsant activity.

Chen et al. (2007) synthesized a series of 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazole derivatives as open-chain analogues of 7-alkoxy-4,5-dihydro[1,2,4] triazolo[4,3-a]quinolines.

Sarro et al. (2000) investigated 7-Nitroindazole, a selective neuronal nitric oxide synthase inhibitor 25-200 mg kg^{-1}, intraperitoneally antagonized audiogenic seizures in DBA/2 mice in a dose-dependent manner.
Obniska et al. (2006a) synthesized a series of N-phenyl- and N-benzyl-2-azaspiro[4.4]nonane- and [4.5]decane-1,3-diones containing a fluoro or trifluoromethyl substituents at the aryl ring and tested for their anticonvulsant activity in the maximal electroshock (MES) and subcutaneous metrazole (sc.Met) tests. Among them, the most active were N-benzyl derivatives with fluoro and trifluoromethyl substituents especially at position-2 of the aryl moiety.

Chimirri et al. (2002) synthesized a series of new 3-ethoxycarbonyl-11H-[1,2,4] triazolo [4,5-c] [2,3]benzodiazepines starting from the corresponding bicyclic 1-aryl-3,5-dihydro-7,8-dimethoxy-4H-2,3-benzodiazepin-4-ones (CFMs), previously described as non competitive AMPA type glutamate receptor antagonists, more potent than GYKI 52466.

De-Sarro et al. (1999) prepared the novel 1-aryl-3,5-dihydro-7,8-methylenedioxy-4H-2,3-benzodiazepin-4-ones (12a-j) and their anticonvulsant effects were evaluated by using various models of experimental epilepsy.

Zarghia et al. (2005) synthesized a series of new 2-substituted-5-(2-benzylxyphenyl)-1,3,4-oxadiazoles and evaluated as anticonvulsant agents.
Akturka et al. (2002) reported in this study that, 15 ω-(1H-imidazol-1-yl)-N-phenylacetamide, propionamide and butyramid derivatives having methoxy, methyl, nitro and chloro in ortho position of N-phenyl ring or without any substituent synthesized by two-step. Their anticonvulsant activity was determined against seizures induced by maximal electroshock (MES).

Obnisk et al. (2009) developed new anticonvulsants, the series of N-[(4-arylpiperazin-1-yl)-alkyl]-3-(2-methylphenyl)- (8a-e,10a-h) and 3-(2-trifluoromethyl-phenyl)-pyrroldine-2,5-diones (9a-e, 11a-i) were synthesized and tested for anticonvulsant activity using the maximal electroshock (MES), subcutaneous pentyleneetrazole (scPTZ) screens.

Shiradkar et al. (2007) synthesized clubbed thiazolidinone-barbituric acid and thiazolidinone-triazole derivatives and screened for anticonvulsant activity.

Nikalje et al. (2007) have synthesized new 1,5-benzothiazepines as potential CNS and CVS agents. A new series of 2-[substituted thiochromon-3'-yl]-4-[2'hydroxy-3'β-substituted phenyl]-2, 3-dihydro-1, 5-benzothiazepine was synthesized. All the compounds screened for their cardiovascular and the CNS depressant activity.

Nikalje et al. (2009) have discussed the various pharmacological activities of thiazolidinone nucleus including anticonvulsant activity, in a review article.

Nikalje et al. (2010) have synthesized novel 1,5-benzothiazepines and evaluated for anticonvulsant activity.
CONCLUSIONS

Despite the development of several new anticonvulsants, the treatment of epilepsy remains still inadequate. About one third of the patients do not respond well to currently available treatment, even if multiple drugs with complementary activities are used. According to a recent prospective study only 63% of cohorts of 525 patients were diagnosed. Furthermore, more than 50% of epilepsy patients experience unwanted side effects of drug treatment such as drowsiness, giddiness, headache etc.

From the literature survey, it is observed that, GABA (γ-amino butyric acid) plays important role as anticonvulsant agents. Based on this observation, the easy synthetic routes for synthesis of GABA modulating agents have taken attention of the chemists, pharmacologists and researchers to find drugs which are more potent, less toxic and at the same time better tolerated than existing drugs.

ACKNOWLEDGMENT

Authors are grateful to the Chairman, Mrs. Fatima Rafiq Zakaria, Maulana Azad Education Trust and Dr. M. H. Dehghan, Principal, Y.B Chavan College of Pharmacy, Aurangabad for their encouragement and support.

REFERENCES


